

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DELTAMETHRIN

Chemical Code # 3010, Tolerance # 51846

Original date: 12/7/95

Revised date: 5/24/00

I. DATA GAP STATUS

Combined, rat:	No data gap; No adverse effect
Chronic toxicity, dog:	No data gap; <b>Possible adverse effect</b>
Oncogenicity, mouse:	No data gap; No adverse effect
Reproduction, rat:	No data gap; No adverse reproductive effect
Teratology, rat:	No data gap; No adverse effect
Teratology, rabbit:	No data gap; No adverse effect
Gene mutation:	No Data gap; No Adverse Effect
Chromosome effects:	No data gap; No adverse effect
DNA damage:	No data gap; No adverse effect
Neurotoxicity:	No data gap; <b>Possible adverse effect</b>

Toxicology one-liners are attached.

All record numbers through 172844 were examined.

\*\* indicates an acceptable study.

Bold face indicates a possible adverse effect.

## indicates a study on file but not yet reviewed.

File name: T000524

Revised by P. Leung, 5/24/00

Data gaps in earlier submission have been filled by bridging to acceptable studies involving the closely related compound, tralomethrin. One-liners for these studies appear at the end of this toxicology summary.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

022 132785 "Two-year Oral Toxicity and Carcinogenicity Study in Rats" (Goldenthal, E., 835, International Research and Development Corporation, Mattawan, MI., 5/6/80) Delta Tech (Deltamethrin, RU 22974, Lot 22, purity 98%) was administered in the feed to 90 Sprague-Dawley rats/sex/dose at levels of 0, 2, 20 and 50 ppm for 2 years; interim sacrifice at 6, 12 and 18 months of exposure with 10 rats/sex/dose; reduced weight gain at 50 ppm; no changes in general behavior, survival, food consumption or gross lesions; dose-related increase in degeneration of sciatic, tibial and plantar nerves seen at 18 month interim sacrifice in mid- and high-dose rats but not at terminal sacrifice; NOEL(M/F)=50 ppm (no effect at HDT); no other non-neoplastic or neoplastic lesions reported; **No Adverse Effects**; NOAEL(M/F)=50 ppm. **UNACCEPTABLE** (inadequate dose level selection, but **possibly upgradeable** with submission of dose level justification). Kellner, 9/13/95.

51846-023:132787 addendum to 51846-022:132785 "Two-year Oral Toxicity and Carcinogenicity Study in Rats" (Kahn, A., 835, International Research and Development Corporation, Mattawan, MI., 5/6/80) Delta Tech (Deltamethrin, RU 22974, Lot 22, purity 98%) was administered in the feed to 90 Sprague-Dawley rats/sex/dose at levels of 0, 2, 20 and 50 ppm for 2 years; supplemental submission concerned additional low and mid-dose testes sections prepared and examined for histopathologic examination to evaluate possible increases in interstitial cell adenoma; a dose-related increase in testicular adenomas was not indicated by the data. **No adverse effects indicated; Supplemental**; Kellner, 9/19/95.

**\*\*085 145603** "Deltamethrin (Technical) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats" (Ryle, P., et al., 835, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England; Study # RSL 814/932275, 12/11/95). Deltamethrin (batch 9N 1239 B2, purity of 98.9%) given orally (feed) to 50 CrI:CD(SD)BR rats/sex/dose (main study) and 20/sex/dose (satellite) at levels of 0, 25, 125, 500 and 800 ppm for 2 years; Clinical Signs (mostly in week 1, largely resolved by week 8) included uncoordinated movement of limbs with limbs splayed (most high-dose males and two females and one male at 500 ppm) and unsteady gait. Body Weight- high-dose males and females and 500 ppm males showed less gain (week 1). Food intake reductions paralleled the decreased weight gain. Increased incidence of eosinophilic hepatocytes (500 and 800 ppm males) and increased incidence of cystic degeneration (or ballooned cells) were noted in males (125 and 800 ppm). NOEL(M)=25 ppm (1.1 mg/kg/day; based on ballooned cells in liver). (F)=125 ppm (7.3 mg/kg/day; unsteady gait, splayed hindlimbs). **No Adverse Effects** [NOAEL(M/F)=800 ppm or M=35.9 mg/kg/day and F=47.1 mg/kg/day]. **ACCEPTABLE**. Kellner, 4/10/96.

### CHRONIC TOXICITY, DOG

**\*\*021 132784** "Deltamethrin (Technical) Toxicity to Dogs by Repeated Oral Administration for 52 Weeks" (Ryle, P., et al., 831, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England; Study # RSL 816/920929, 10/21/93). Deltamethrin (batch 9N1239 B2, purity of 98.9%) given orally (gelatin capsule) to 4 beagle dogs/sex/dose at levels of 0, 1, 10, 50 mg/kg/day for 52 weeks; Observations-(at 50 mg/kg) unsteadiness, body tremors, abnormal head movements, vomiting, liquid feces, reduced weight gain and food consumption; (at 10 mg/kg) unsteadiness and increased liquid feces; Neurological exams-trembling and abnormal gait (high-dose); NOEL(M/F)=1 mg/kg/day (based on tremors); **Possible Adverse Effect**; NOAEL(M/F)=1 mg/kg/day (based on tremors); **ACCEPTABLE**. Kellner, 9/18/95.

## ONCOGENICITY, MOUSE

024 132788 "Two-year Oral Toxicity and Carcinogenicity Study in Mice" (Goldenthal, E., 832, International Research and Development Corporation, Mattawan, MI., 5/6/80) Deltamethrin (Deltamethrin, RU 22974, Lot 22, purity 98%) was administered in the feed to 80 CD<sup>7</sup>-1 mice/sex/dose at levels of 0, 1, 5, 25 and 100 ppm for 2 years; interim sacrifice of 10 mice/sex/dose after 12 and 18 months; no changes in weight gain, general behavior, survival, food consumption or gross lesions; NOEL(M/F)=100 ppm (based on no effect at HDT); no non-neoplastic or neoplastic lesions reported; **No Adverse Effects Indicated**; NOAEL(M/F)=100 ppm. **UNACCEPTABLE** (inadequate dose level selection, but **possibly upgradeable** with submission of dose level justification). Kellner, 9/13/95.

\*\*086 145604 "97-Week Carcinogenicity Study by Oral Route (Dietary Admixture) in Mice" (Richard, J., 832, Centre International de Toxicologie (C.I.T.), Miserey, France; Study # 7347 TCS, 12/26/95). Deltamethrin (Lot/Batch 1N0187B2 and 2N0398B2, purity of 98.0%) was given orally (feed) to 50 Crl:CD-1(ICR)BR mice/sex/dose at levels of 0, 10, 100, 1000 or 2000 ppm for 97 weeks. Mortality- slight increase in female mortality after week 78 (i.e., equivocal effect); emaciation and dyspnea were noted a few weeks before death. Cutaneous lesions (i.e., sores, scars or scabs) on various parts of the body in both treated and control animals. NOEL(M/F)=100 ppm (based on increased number of dermal lesions at 1000 and 2000 ppm). Body Weight- high-dose males showed slightly less body weight gain compared to controls during the first year of treatment (between weeks 26 and 46). Microscopic pathology (non-neoplastic findings)- increased incidence of ulceration of the skin together with cellulitis; **No Adverse Effects** [NOAEL(M/F) = 2000 ppm]. No neoplastic findings; no increase in the incidence of spontaneously occurring tumors or decrease in the latency of tumor appearance was noted at any dose level. **ACCEPTABLE**, Kellner, 4/12/96.

## REPRODUCTION, RAT

014 129682 "Three Generation Reproduction Study in Rats" (Wrenn, J., International Research and Development Corporation, Mattawan, MI. IRDC Study # 406-003, 2/5/80). Deltamethrin technical (lot 22, purity not stated) was administered in the diet to 10 male and 20 female Charles River CD\* rats/dose/generation beginning about 76 days before mating and continuing through sacrifice at levels of 0, 2, 20 and 50 ppm for three generations; decreased mean parental body weight of the F0 males in the 50 ppm dosage group; slight reductions in mean food consumption in 50 ppm F1 males and F2 females; Parental NOEL = 20 ppm; reduced mean pup body weights at lactation day 21 in F1, F2 and F3 litters. **No Adverse Effects** (no reproductive toxicity at any dosage level tested); Reproductive NOEL=50 ppm; **UNACCEPTABLE** but **possibly upgradeable** with submission of test article purity, adequate dose level justification and full histopathology of parental animals. Kellner, 7/21/95.

\*\* 136; 172624; "Deltamethrin: Reproductive Effect of Deltamethrin Administered Orally in the Diet to Crl:CDBR VAF/Plus Rats for Two Generations"; (A.M. Hoberman; Argus Research Laboratories, Inc., Horsham, PA; Project ID. 818-001; 1/17/92); Thirty rats/sex/group were dosed in the diet with 0, 5, 20, 80 or 320 ppm of Deltamethrin technical (purity: 99.7%) for two generations. The treatment period for the P1 parents included 82 days prior to mating, the mating period, 3 weeks of gestation and 3 weeks of lactation. At that time, 30 F1 animals/sex/group were selected as parents and treated for a minimum of 86 days in the pre-mating period, the mating period, and 3 weeks both for the gestation and lactation periods. For the P1 generation, one female in the 320 ppm group died as a result of the treatment. The only clinical signs exhibited by the P1 generation were the high dose females during the lactation period when the uptake of the active ingredient was at the highest level. These signs included ataxia and hypersensitivity. The high dose group for the F1 generation suffered 17 male and 19 female treatment-related mortalities between days 2 and 44 of the pre-mating period. Clinical signs manifested by these animals included ataxia, urine stained abdominal fur, impaired righting reflex, splayed limbs and vocalization. The signs became less severe as the animals aged and consumed a lower relative quantity of the test material. The mean body weights and food consumption values of the 320 ppm treatment group of both generations were lower than those of the controls (p<0.01). Although the absolute and relative organ weights were significantly reduced or increased in comparison to the control values, there was no

apparent treatment-related effect upon any of these organs. The gross examination revealed that 9/28 males and 12/28 females in the F1 high dose group suffered blood clots in either the subdural or epidural region of the brain. All of these animals died between day 2 and 44 of the prepartum period. There were no treatment-related effects upon the reproductive parameters. The mean pup weights for the high dose group in both generations were not significantly different from those of the controls at the time of birth. However, by day 7 of the lactation period, the mean weights of these pups were less than those of the controls ( $p < 0.01$ ). In addition, the F1 pups in the 320 ppm treatment group suffered increased mortality between days 4 and 21 of lactation. This effect was not evident in the F2 group. **No adverse reproductive effects** indicated. **Parental NOEL:** 80 ppm (based upon the clinical signs, increased mortality, lower body weight and reduced food consumption noted for the 320 ppm treatment group) ((M) 5.4 to 5.8 mg/kg/day, (F) 5.2 to 10.6 mg/kg/day), **Reproductive NOEL:** 320 ppm (no treatment-related effect on reproductive parameters at highest dose tested) ((M) 21.2 to 24.9 mg/kg/day, (F) 21.8 to 37.3 mg/kg/day), **Developmental NOEL:** 80 ppm (based upon lower mean pup body weights for both generations and increased mortality for the F1 pups during the lactation period in the 320 ppm treatment group); Study **acceptable**. (Moore, 2/3/00)

#### TERATOLOGY, RAT

\*\*005 129659 "Developmental Toxicity Study of Deltamethrin in Rats" (Schardein, J. International Research and Development Corporation, Mattawan, MI. IRDC Study # 327-120, 7/6/90). Deltamethrin technical (lot 8N 0701 B2, purity of 99.2%) was administered by oral gavage to 25 mated female Crl:CD® VAF/Plus rats/sex/dose at levels of 0 (2 groups), 1 (2 groups), 3.3 (2 groups), 7 and 11 mg/kg/day; Mortality- (deaths and moribund sacrifice) at 3.3, 7 and 11 mg/kg/day were 1, 1 and 14, respectively, although death at 3.3 mg/kg probably not compound-related; observations- (high-dose) convulsions (9/25), anogenital staining (5/25), abnormal vocalization (3/25), sensitive to external stimuli (6/25); weight gain- reduced maternal weight gain at mid- and high-dose levels; maternal NOEL = 3.3 mg/kg/day; **No Adverse Effects**; Developmental NOEL = 11 mg/kg; **ACCEPTABLE**. Kellner, 7/18/95.

#### TERATOLOGY, RABBIT

\*\*004 129658 "Developmental Toxicity Study of Deltamethrin in New Zealand White Rabbits" (Schardein, J. International Research and Development Corporation, Mattawan, MI. IRDC Study # 327-112, 5/7/90). Deltamethrin technical (purity of 99.2%, lot 8N 0701 B2) was administered by oral gavage to 16 inseminated New Zealand White SPF female rabbits/dose at levels of 10, 25 and 100 mg/kg/day. Mortality- one high-dose doe died on gestation day 27 with congestion of the lungs; death at 10 mg/kg/day not considered compound-related; maternal NOEL = 25 mg/kg/day (based on mortality at high dose); Fetal morphology- no dose-related malformations; variations (high-dose) included wrist flexure and retardation of ossification in hyoid body, pubic bones and unossified tail bones. Developmental NOEL = 25 mg/kg (based on retardation of bone ossification); NOEL(M/F)=100 mg/kg/day; **No Adverse Effects**; **ACCEPTABLE**. Kellner, 7/18/95.

#### GENE MUTATION

003 129657 "Mutagenic Activity of the Product RU 22974 with Schizosaccharomyces Pombe" (842, Mondino, A., Antoine Marxer RBM Institute of Biomedical Research, no Laboratory Study #, 12/12/79) Deltamethrin technical (purity not specified, batch # 6E0660) was tested in Schizosaccharomyces Pombe at levels of 0, 250, 500 and 1000 mg/L with and without microsomal S-9 metabolic activation; **No Adverse Effects**; no increases in genetic mutations at any dose tested; **UNACCEPTABLE, not upgradeable**; lack of reporting of key data, compound content in the dosing solutions unclear, lack of replicates, description of exposure conditions incomplete (i.e. verification of dose levels applied was not possible from the description provided). Kellner, 7/17/95.

51846-208; 174539A; "Detection of a Mutagenic Potency of Decamethrin (RU 22974) Bacterial Tests" (Chantot, J., et al., Centre de Recherches Roussel-Uclaf, 93230 Romainville, France, Project ID No. RU/Tox/80.21.01/A, 1/21/80). DNA repair-deficient E. coli strains CM 611 (uvrA<sup>-</sup>, exrA<sup>-</sup>) and p 3478

(pol A) were tested for growth inhibition, relative to their repair-proficient counterparts, during exposure to test article Decamethrin (purity and Lot No. not provided). Concentrations from 0 (DMSO) to 5000 ug/ml were tested. Exposure was for 18 hrs at 37°C. Each concentration was tested in 9 replicate wells/dish/bacterial strain. One trial was conducted. Areas of growth inhibition were measured and the areas of repair-deficient inhibition/repair-proficient inhibition were calculated. The positive control (MNNG) gave ratios from 1.66 to 2.1, as expected for a compound which inhibits growth by damaging DNA. In contrast, the negative control (chloramphenicol) gave ratios from 0.81 to 0.88, indicative of a compound which causes similar growth inhibition in DNA repair-deficient and proficient strains. The test article did not significantly inhibit the growth of either the repair-deficient or proficient strain. Therefore, it was considered nonmutagenic in the assay. **No adverse effects indicated. Study unacceptable and not upgradeable** due to a failure to perform the assay under activating conditions (Vidair 5/8/00).

51846-208; 174539B; "Detection of a Mutagenic Potency of Decamethrin (RU 22974) Bacterial Tests" (Chantot, J., et al., Centre de Recherches Roussel-Uclaf, 93230 Romainville, France, Project ID No. RU/Tox/80.21.01/A, 1/21/80). Test article Decamethrin (Batch No. 28, purity = 99%) was evaluated for its ability to induce reversion to histidine prototrophy in Salmonella typhimurium tester strains TA98, TA1537, TA1538 (reverted by frameshift mutations), TA100 and TA1535 (reverted by base substitutions). Concentrations of test article, from 0 to 5000 ug/plate, were evaluated in 4 replicate plates, both in the presence and absence of an activating S9 microsomal fraction. Exposure to the test article was for 2-3 days at 37°C. At  $\geq 200$  ug/plate, some precipitation of test article was observed. Some cytotoxicity was seen at "very high concentrations", as shown by smaller revertant colony size. The test article caused no dose-dependent increases in the background revertant frequency. In contrast, positive controls were functional. Therefore, the test article was judged nonmutagenic in the assay. **No adverse effects indicated. Study acceptable** (Vidair 5/8/00).

#### CHROMOSOME EFFECTS

\*\*003 129655 "Chromosome Aberration Assay of Deltamethrin in Chinese Hamster Ovary (CHO) Cells" (842, Putman, D. and Morris, M., Microbiological Associates, Inc., Rockville, Md, Study #T8418.337003, 2/23/89). Deltamethrin technical (purity of 99.2%, lot # 8B-0153B3) was tested in Chinese hamster ovary (CHO) cells with and without metabolic activation by Aroclor 1254-stimulated rat liver S-9 fraction, with 2 cultures/dose in 2 activated trials (8 and 12 hr. harvest following a 2-hr exposure period) and 1 non-activated trial (18 hr. harvest) at doses of 0, 19, 38, 75 and 150 ug/ml; **No Adverse effects**; no increase in proportion of aberrant metaphases at any dose level; **ACCEPTABLE**. Kellner, 7/10/95.

#### DNA DAMAGE

\*\*003 129656 "Unscheduled DNA Synthesis of Deltamethrin in Rat Primary Hepatocytes" (844, Curren, R., Microbiological Associates, Inc., Rockville, Md, Study #T8418.380, 3/13/89). Deltamethrin technical (purity of 99.2%, lot # 8B-0153B3) was tested in rat primary hepatocytes at seven dose levels ranging from 4.2 to 4200 ug/ml (fully evaluated at 42, 130, 420, 1300 and 4200 ug/ml); **No Adverse Effects**; no increases in the mean number of net nuclear grain counts at any dose tested; **ACCEPTABLE**. Kellner, 7/14/95.

#### NEUROTOXICITY

010; 129665; "RU 22974 (Decamethrin) LD50 Determination and Assessment of Neurotoxicity in the Domestic Hen" (Authors: Ross, David B., et al; Huntingdon Research Centre, Huntingdon, England; Lab Report No. RSL 293-NT/7830/A; 1/19/78); 817; Decamethrin (RU 22974; Cle: 6E0660; purity not reported), dosed as 5-40% (w/v) suspensions/solutions in corn oil or sesame oil; 10 hens/dose level; IN CORN OIL: 0 (vehicle), 0 (500 mg/kg TOCP), 500, 1250, 5000 mg/kg; Mortality- 0/10, 8/10, 0/10, 0/10, 0/10; IN SESAME OIL: 0 (vehicle), 1000 mg/kg; Mortality- 0/10, 2/10; no clinical or histological signs of neurotoxicity; positive controls were responsive; **no adverse effects; Unacceptable and cannot be upgraded** because negative results were not confirmed by a second dose and observation period. (Duncan, 7/6/95)

**\*\* 51846-121 162894** An Acute Oral Neurotoxicity Study of Deltamethrin in Rats" (Nemec, M.D., WIL Research Laboratories, Inc., Ashland, OH, Laboratory Study No. WIL-274002, 3/18/98). 818. Deltamethrin Technical (Batch No. 4N0397B, purity=99.2%), prepared in corn oil, was administered by gavage in a single dose at concentrations of 0 (vehicle), 5, 15, and 50 mg/kg to 12 Sprague-Dawley CrI:CD®BR rats per sex per dose level. One male and one female at 50 mg/kg died on Day 0. 3 hours following dosing on Day 0 FOB assessments revealed treatment-related altered posture (home cage), convulsions (home cage), tremors (home cage and open field), biting (home cage), eyelids slightly drooping (home cage), decreased ease in removal from cage and ease of handling, severe salivation during handling, slightly soiled fur, increased mean time to first step (open field), moderately impaired mobility (open field), hindlimbs splayed or dragging (open field), clonic and tonic convulsions (open field), severe impairment of gait (open field), low arousal and writhing (open field), decreased mean number of rears (open field), no reaction in approach, touch, and tail pinch response tests, and in olfactory orientation, landing on back or side during air righting reflex test, decreased mean forelimb and hindlimb grip strength, decreased rotarod performance, decreased mean hindlimb footsplay (males only), decreased mean body temperature, and increased catalepsy at 50 mg/kg in both males and females with all signs clearing by Day 7 except for mean hindlimb footsplay in males that demonstrated a treatment-related increase at Day 7 but cleared by Day 14. A statistically significant increase in total mean number of activity counts in both total motor activity and ambulatory activity in males at 50 mg/kg on Day 0 was observed clearing by Day 7. Necropsy and microscopic examination revealed no treatment-related abnormalities on the surviving animals. **Possible adverse effect indicated:** tremors and convulsions during FOB assessments. NOEL (M/F)=15 mg/kg (based on observations made during FOB). Previously considered unacceptable but possibly upgradeable with verification that the same individual(s) who conducted the positive control studies is (are) the same individuals who conducted this acute neurotoxicity study. (Corlett and Leung, 12/1/98). Letter of Feb. 16, 1999 stated that all technical personnel involved in acquiring data on the deltamethrin studies participated in the inter-observer reliability studies. Study upgraded to **acceptable**. (Kellner, 3/30/99).

**\*\* 51846-122; 162895;** A Subchronic (13-Week) Neurotoxicity Study of Deltamethrin in Rats" (Nemec, M.D., WIL Research Laboratories, Inc., Ashland, OH, Laboratory Study No. WIL-274003, 3/19/98). 827. Deltamethrin Technical (Batch No. 4N0397B, purity=99.2%) was admixed to the feed at concentrations of 0, 50, 200, or 800 ppm (0, 4, 14, or 54 mg/kg/day, respectively, for males and 0, 4, 16, or 58 mg/kg/day, respectively, for females) and fed to 10 CrI:CD®(SD)BR rats per sex per dose level continuously for a period of at least 91 consecutive days. 3 males and 3 females at 800 ppm died or were euthanized in extremis. Treatment-related clinical signs of rocking, lurching, or swaying while walking, hypersensitivity to noise, walking with hindlimbs splayed, impaired righting reflex, and walking on tiptoes were observed at 800 ppm. FOB assessments revealed treatment-related impaired mobility, ataxia, and impaired gait (open field, males and females, Weeks 3, 7, and 12), side to side rocking (open field, males and females, Weeks 7 and 12), slightly impaired air righting reflex (males and females, Weeks 7 and 12), reduced hindlimb extensor strength (males and females, Weeks 3, 7, and 12), and reduced forelimb and hindlimb grip strength (males, Week 3) at 800 ppm. No treatment-related effects were observed during motor activity assessments. No treatment-related effects were observed at gross necropsy or during microscopic examination in the surviving animals. **Possible adverse effect:** ataxic gait. NOEL (M)=14 mg/kg/day (200 ppm) and (F)=16 mg/kg/day (200 ppm) (based on decreased mean body weight and numerous FOB observations). Previously considered unacceptable but possibly upgradeable with verification that the same individual(s) who conducted the positive control studies is (are) the same individuals who conducted this subchronic neurotoxicity study. (Corlett and Leung, 12/8/98) Letter of Feb. 16, 1999 stated that all technical personnel involved in acquiring data on the deltamethrin studies participated in the inter-observer reliability studies. Study upgraded to **acceptable**. (Kellner, 3/30/99).

#### SUBCHRONIC STUDIES

006 129660 "RU 22974 Assessment of Toxicity to Rats by Oral Administration for 13 Weeks (followed by a 4-week withdrawal period)" (Hunter, B., 821, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, 3/21/77) Delta Tech (Deltamethrin, RU 22974, Lot 17, purity > 99%) was

administered by oral gavage 20 Sprague-Dawley rats/sex/dose at levels of 0, 0.1, 1.0, 2.5 and 10.0 mg/kg/day for 13 weeks (plus 4 week withdrawal period for 5 rats/sex/dose); Observations- (10 mg/kg) hypersensitivity in males by week 6, recovery by week 13 without any change in food consumption; reduced weight gain during 13 weeks in 2.5 mg/kg and high-dose males. Nominal NOEL(M)=1.0 mg/kg/day (based on decreased body weight gain), (F)=10 mg/kg/day (no effect at HDT); **No Adverse Effects**; NOAEL(M/F)=10 mg/kg/day; **ACCEPTABLE**; Kellner, 7/21/95.

51846-138; 172844; "Deltamethrin Toxicity Studies in Rats for Dietary Administration for 13 Weeks with a 4-Week Recovery Period"; (P.R. Ryle et. al.; Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England; Study No. RSL 813/827/901757; 7/3/91); Twenty Crl:CD(SD)BR rats/sex/group were treated in the diet with 0, 30, 300, 3000 or 6000 ppm of Deltamethrin Technical (Batch # 9N1239B2; purity: 98.9%) for 13 weeks ((M): 0, 2.4, 23.9, 241 and 425 mg/kg/day, (F): 0, 2.7, 30.5, 272, and 444 mg/kg/day). Ten of the animals/sex/group were retained for a 4-week recovery period. Due to the complete mortality of the 3000 and 6000 ppm groups within 3 weeks of the study's initiation, a supplemental study was undertaken in which 20 animals/sex/group were treated in the diet to 0 or 1000 ppm of the test material ((M): 0, 72.1 mg/kg/day, (F): 0, 83.9 mg/kg/day). Ten of these animals/sex/group were retained for a 4-week recovery period. In the 1000 ppm treatment group, one male and two females were euthanized in extremis as well, two on day 13 and the other during the fifth week. Clinical signs were exhibited by animals in the 1000 ppm treatment group and above. These signs included incoordinated movement, unsteady gait, hunched posture, increased sensitivity to sound, gasping, body tremors, shuffling on abdomen, piloerection, spasmodic convulsion, "wet dog" shakes and wet urogenital fur. The mean body weight gain for the females was less than the control for all of the treatment groups ( $p < 0.05$  or  $p < 0.01$ ). For the males, the mean body weight gain in the 1000 ppm treatment group was lower than that of the controls ( $p < 0.01$ ). Mean food consumption was affected by the treatment for the 3000 and 6000 ppm groups ( $p < 0.01$ ). There were no apparent treatment-related effects upon the ophthalmology, hematology, clinical chemistry or urinalysis values. Gross examination of the animals at the termination of the study did not reveal any treatment-related lesions. The animals which died on study (3000 and 6000 ppm treatment groups) exhibited enlarged cervical lymph nodes, minimal adipose tissue, gaseous distension of the gastrointestinal tract, pale spleen, small seminal vesicles and prostate and thin uterus. These animals were not examined histologically. There were no apparent treatment-related lesions in the histopathologic examination of the organs and tissues of the 1000 ppm treatment group. Target organ: central nervous system; **Possible adverse effects**: neurotoxicity; NOEL: (M) 300 ppm (23.9 mg/kg/day, (based upon the reduced body weight gain and clinical signs exhibited by the males in the 1000 ppm treatment group), (F) < 30 ppm (2.7 mg/kg/day) (based upon the lower body weight gain for the females in the 30 ppm treatment group). Study **acceptable**. (Moore, 2/17/00)

\*\*009 129664 "21-Day Dermal Toxicity Study in Rats with Deltamethrin Technical" (Siglin, J., 822, Springborn Laboratories, Inc. (SLS), Spencerville, OH; SLS Study # 3207.28, 4/9/93). Deltamethrin was administered to 5 rats/sex/dose at levels of 0, 100, 300 and 1000 mg/kg for 21 days; Observations- dermal irritation at all dose levels; slight reduction in weight gain and food consumption during days 1-8 in 300 and 1000 mg/kg males; Histopathology- limited to dermal changes including dermal abscesses, chronic dermatitis, exudate on the epidermal surface and mononuclear cell foci in the dermis; NOEL(M/F)<100 mg/kg (based on dermal changes); **No Adverse Effects**; NOAEL(M/F)=1000 mg/kg/day; **ACCEPTABLE**. Kellner, 7/18/95.

50665-093; 142481; Deltamethrin - Oral Toxicity Study in Beagle Dogs (Final Report - repeated daily dosage for 13 weeks with a 4-week recovery period for selected animals)" (P. R. Ryle, et. al., Huntingdon Research Centre Ltd., Cambridgeshire, UK, RSL 829-G.901755, 7/8/91); Deltamethrin Technical (Batch # 9N1239 B2, 98.9% purity) administered orally in gelatin capsules to 3 dogs/ sex/dose at 0 (empty gelatin capsule), 2, 10, or 50 mg/kg/day for 13 weeks; 3 extra dogs/sex were added to the control and high dose groups for a 4-week recovery period; all animals survived the study until scheduled sacrifice; possible adverse effects; clinical signs including body tremors (9/12 dogs), unsteady gait (1.5 to 7 hrs after dosing), vomiting (1 to 6 hrs post dose, weeks 1 to 6) were noted in high dose animals; reduced body weight gain and food consumption were reported in animals receiving 50 mg/kg/day; no treatment-related clinical signs or body weight changes were detected during the recovery period; no changes in hematology, clinical chemistry, urinalysis, ophthalmology, necropsy and histopathology

attributable to deltamethrin treatment were observed; NOEL (M/F) = 10 mg/kg/day (based on clinical signs); NOAEL (M/F) = 10 mg/kg/day (based on body tremors); **acceptable**; (Leung, 11/14/95).

**\*\*007 129661 "RU 22974 Oral Toxicity Study in Beagle Dogs"** (Chesterman, H. 821, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. Study RSL 253/77251, 6/9/77). Deltamethrin (lot 17, purity > 99%) given orally (dissolved in PEG 200 and inserted into gelatin capsule) to 4 to 6 beagle dogs/sex/dose at levels of 0, 0.1, 1.0, 2.5 and 10.0 mg/kg/day for 13 weeks (plus 20 week recovery for 2 dogs/sex in three highest dose groups); Observations- (10 mg/kg) unsteadiness, body tremors (Possible adverse effect), jerking movements, vomiting, excessive salivation, liquid feces, dilation of the pupils; reduced weight gain and food consumption during first 1-2 weeks of dosing; neurological exams- depression of the flexor reflex and exaggeration or depression of the patellar reflex, NOEL(M/F)=0.1 mg/kg (based on depressed patellar reflex); EEG (Dosing Period)- abnormal EEGs (persistent high amplitude, fast frequencies with spikes) in one dog at 2.5 mg/kg/day and three receiving 10 mg/kg/day after 12 weeks of exposure; EEG (Recovery Period)- abnormal wave patterns with spiking in all leads was seen in 2 of 4 high-dose recovery dogs; NOAEL(M/F)=2.5 mg/kg/day (based on body tremors); **ACCEPTABLE**; Kellner, 7/25/95.

**008 129663 "RU 22974 (DECIS) Inhalation Toxicity Study in Rats 14 x 6 Hour Exposures Over a Period of 3 Weeks"** (Coombs, D., et al., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report #: RSL 318/78638, 3/21/77); Delta Tech (Deltamethrin, RU 22974, Lot 22, unknown purity) was administered by inhalation 6 hours/day, 5 days/week for 2 weeks and 4 days on the 3rd week (14 exposures total) to 8 CD\* rats/sex/dose at levels of 0, 1, 10 and 50 mg/m<sup>3</sup>; Observations- reactions to dust (licking mouth and blinking) at all levels, peripheral vasodilation (mid- and high-dose), scratching with ptialism (all levels); **Possible Adverse Effect Indicated:** ataxia and walking with arched backs (high-dose); No treatment-related changes in organ weights were reported; although small but statistically significant changes in urine volume, pH, specific gravity, hematocrit, RBC counts, serum sodium levels and BUN were reported, they were within historical control levels and were not considered to be toxicologically significant; NOEL(M/F)<1 mg/m<sup>3</sup> (based on reaction to dust at all levels); NOAEL(M/F)=10 mg/m<sup>3</sup> (ataxia in high dose animals); **Supplemental**; Kellner, 7/24/95.

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## METABOLISM STUDIES

**\*\*012 129680, "Metabolism of 14C-Deltamethrin in Rats"** (Bosch, A., Hazleton Laboratories America, Inc., Madison, WI, HLA Study #6187-108, 7/9/90). Unlabeled RU22974 (lot# 7B0235B, 99.3% purity), 14C-Benzyl-(lot# X6819A, 59.2 mCi/mmol, 95% purity) or 14C-Dimethyl-(lot# X7506A, 60 mCi/mmol, >95% purity) RU22974; administered by oral gavage to 5 Crl:CD<sup>®</sup>(SD)BR rats/sex/dose at 0.55 mg/kg (single oral dose), 0.55 mg/kg (14 nonradiolabeled doses followed by a radiolabeled dose on day 15) and 5.50 mg/kg (single oral dose); most of the radioactivity excreted in the urine (31% to 56%) and feces (36% to 59%) after 168 hrs postdose; tissue and carcass residues less than 2% of dose at 7 days, with fat containing highest concentrations; rats dosed with 14C-benzyl deltamethrin, 30% to 49% excreted in the the urine as 4'SO<sub>2</sub>-mPBAcid and 2% to 4% as unconjugated mPBAcid; 17% to 46% in feces as deltamethrin (the higher dosage rats excreted a higher percentage in the feces as deltamethrin and a lower percentage in the urine as 4'SO<sub>2</sub>-mPBAcid); for rats dosed with 14C-Dimethyl deltamethrin, 22% to 38% of the dose was excreted in the the urine as Br<sub>2</sub> CA-glucuronide and 4% to 10% as the unconjugated Br<sub>2</sub> CA; 21% to 35% was excreted in the feces as deltamethrin. **ACCEPTABLE**. Kellner, 8/31/95.013 129681, "Metabolism of 14C-Tralomethrin in Rats" (Tanoue, T., 851, Environmental Toxicology Laboratory, Nippon Soda Co., LTD., Odawara, Japan. Study #'s EC-151, -160, -169, -172, 11/11/88, 3/27/89, 6/16/89 and 7/14/89). [Acid-14C]-, [Alcohol-14C]- and [CN-14C]-tralomethrin and [acid-14C]deltamethrin (lot or purity not specified) were given orally (except for one test performed i.v.) to groups of 5 to 12 SD-strain rats/sex/labeled compound at levels of 0.3 and 5.7 mg/kg; Blood levels of radioactivity reached peak at 4 to 6 hours after p.o. dosing with the acid-14C and alcohol-14C; 9 to 24 hours with the CN-14C-; acid-14C and alcohol-14C forms went from a maximum concentration of 75 to 250 ppb to about 1 ppb at 72 hr; high-dose (5.7 mg/kg) tralomethrin rapidly metabolized; metabolites were excreted within 4 days (males: 35.8% in urine and 62.7% in the feces;

females: 46.8 and 50.7% in the urine and feces, respectively); rats retained only 1.5 and 2.5% of the total recovered radioactivity, respectively, after 4 days. Elimination  $t_{1/2}$  were less than 10 hours except for fat and hair (20 to 50 hr). At 168 hours, residue levels were 1330 ppb in hair, 77 ppb in skin and hair and less than 100 ppb in the remaining tissues tested; Major metabolites of tralomethrin include: deltamethrin, Br<sub>2</sub>, Br<sub>2</sub>CA-b-glucuronide, PB acid, 4'-OH-PB acid, PB acid glycine, 4'-OH-PB acid sulfate and SCN. **SUPPLEMENTAL DATA.** Kellner, 8/31/95.

\*\*51846-036; 91524; "Metabolism of 14C-Tralomethrin in Rats" (Hazleton Laboratories America, Inc., Madison, WI, Lab. Project No. HLA 6298-100, 4/5/90); 851; 14C-Tralomethrin (14C-Benzyl, 14C-dimethyl, 59.2-60.0 mCi/mmol, >95% purity); nonlabeled Tralomethrin (lot # 87-72, 98.7% purity); oral; Single (0, 0.75, 7.5 mg/kg), multiple (0.75 mg/kg) dosing qd @ 14 days; 5 rats/sex/dose; no mortalities reported; majority of the radioactivity eliminated in urine (15 - 65%) and feces (22 - 76%) within 24 hours after dosing; low amounts of radioactivity retained in tissues and carcasses at 7 days post-dose and represent 0.48 - 1.5% of dose; highest radioactivity levels found in fat; parent compound not detected in any urine or feces samples examined; deltamethrin present in feces but not in urine suggesting rapid debromination of Tralomethrin in the GI tract followed by cleavage of the ester bond; study **acceptable**; (Leung, 2/5/91).

51846-002, 030; 37515, 37516, 37517, 37563, 37564; "Pyrethroid Metabolism: Comparative Fate in Rats of Tralomethrin, Tralocyrthrin, Deltamethrin, and (1R,aS)-cis-Cypermethrin. (J. Agri. Food Chem. 30 : 631-636, 1982)," (Pesticide Chemistry and Toxicology Laboratory, Dept. of Entomological Sciences, University of California, Berkeley, CA); male Sprague-Dawley rats (no number) orally dosed with 0.30 mg/kg 14C-acid, 14C-alcohol, or 14C-cyano form of tralomethrin dissolved in diethyl ether/partial hydrogenated soybean oil mixture (1:2, v/v); 43%-60% and 39%-56% of the administered radiolabelled dose was excreted in urine and feces, respectively; 0.1% of the 14CN-labelled dose was present in expired CO<sub>2</sub>; majority of 14C activity was excreted in the first 72 hours after administration; tralomethrin undergoes rapid and essentially complete debromination to form deltamethrin; deltamethrin is then hydroxylated at the 2', 4', and 5 positions of the alcohol moiety and the methyl group trans to carboxylate linkage; extensive ester cleavage of deltamethrin yield series of alcohols and carboxylic acids and their glucuronide, glycine, and sulfate conjugates; high levels of 14C-cyano residues detected in skin and stomach 7 days after dosing; **Supplemental**; (Gee, 12/20/85; updated, Leung, 4/11/91).

## TRALOMETHRIN

### COMBINED, RAT

\*\* **004-017, -032, -035; 37498-37499, 37522-37533, 44434, 91521**; "24-Month Oral Toxicity and Oncogenicity Study in Rats" (International Research and Development Corp., Mattawan, MI, Study No. 406-022, 3/9/84); 835; RU 25474 (98.5% purity); oral gavage; 0 (control 1), 0 (control 2), 0.75, 3.0, or 12.0 mg/kg/day in corn oil to 60 - 80 rats/sex/dose for 104 weeks; marked decreases ( $p < 0.05$ ) in body weight gain at high dose 21.2 - 22.7% for males and 6.6 - 9.1% in females without parallel reduction in food consumption; mid-dosed rats showed slight reduction in body weight gain; **possible adverse effects**; clinical observations: excessive salivation (32 week to termination), unable to support weight on limbs, extended limbs laterally from body, and uncoordinated involuntary movement (62 week to termination) at high dose; no treatment-related effects reported in hematologic parameters, biochemistry, urinalysis, organ weights, and incidences of non-neoplastic and neoplastic lesions; no test article-related changes in macroscopic and microscopic pathology; NOEL (M/F) = 3 mg/kg/day (based on clinical observations and decreased body weight gain); initially reviewed as unacceptable but possibly upgradeable (Van Way and Apostolou, 12/24/85); study rereviewed with results from analysis of test solutions, dose level justification, and legible graphs; **acceptable** (upgraded, Leung, 2/20/91; revised, Leung, 3/23/95).

### CHRONIC TOXICITY, DOG

\*\* **027, -032, -033; 37543, 44433, 91519**; "One-Year Oral Toxicity Study in Dogs" (International Research and Development Corp., Mattawan, MI, Study No. 406-023, 9/29/82); 831; RU 25474 (batch 18, OE-0246, 98.5% purity); oral capsule; 0 (corn oil), 0.75 (increased to 1.0 on week 14), 3.0, or 10.0 mg/kg (reduced to 8 mg/kg on week 4, to 6 mg/kg on week 14); 6 dogs/sex/dose; mortality: one

high-dose female died on week 3; **possible adverse effects indicated:** tremors, ataxia and convulsions at 10 mg/kg/day which persisted throughout the study even when the dose level was reduced to 8 mg/kg and then to 6 mg/kg; irregular heart rhythms in high dose dogs; no toxicologically significant changes were reported for hematology, biochemistry, body and organ weights, necropsy and histopathology; NOEL (M/F) = 1 mg/kg/day (0.75 mg/kg/day until up to week 14; tremors and convulsions); study initially reviewed as unacceptable but possibly upgradeable with submission of dosing solution analyses for stability, homogeneity, and content (Shimer and Martz, 12/20/85); study rereviewed with results from analyses of dosing solution for content, stability, and homogeneity; **acceptable;** (upgraded, Leung, 3/5/91).

#### ONCOGENICITY, MOUSE

**\*\* 019-025, -032, -035; 37534-37541, 44436, 91523;** "24-Month Oral Oncogenicity Study in Mice" (International Research and Development Corp., Mattawan, MI, Study No. 406-021, 1/9/85); 832; RU 25474 (98.5% purity); oral gavage; 0 (control 1), 0 (control 2), 0.75, 3.0, or 10.0 mg/kg/day in corn oil to 60 - 80 mice/sex/dose for 104 weeks; clinical observations: uncoordinated involuntary movements (males only), excessive salivation (week 45 to termination), and marked decrease in survival rate at high dose (27% vs. 55% for 10 and 0 mg/kg/day, respectively); **possible adverse effects;** dose-related increased ( $p < 0.05$ ) incidences of dermatitis in all treated groups for males and in high dose for females; with the exception of increased food and water consumption and urine volume at the HDT, there were no treatment-related effects reported in hematologic parameters, biochemistry, urinalysis, organ and body weights; no evidence of oncogenic effects; NOEL (M) < 0.75 mg/kg/day, (F) = 3.0 mg/kg/day (based on incidence of dermatitis); study initially reviewed as unacceptable but possibly upgradeable (Hughett and Christopher, 12/23/85); study rereviewed with revised pathology report; **acceptable** (upgraded, Leung, 2/25/91; revised, Leung, 3/23/95)

018; 37534; "8-Week Oral Range-Finding Study in Mice" (International Research & Development Corp., Mattawan, MI, IRDC-4BE-406.020/A, 10/28/80); RU 25474 (Lot 12, purity not reported); oral gavage; 0 (corn oil), 5, 10, 15, 20, or 30 mg/kg/day to 10 CD-1 mice/sex/dose for 8 weeks; mortality: 20/20, 14/20, and 4/20 mice died during the first week receiving 30, 20, or 15 mg/kg/day, respectively; **possible adverse effects indicated:** dose-related increase in extent, severity and frequency of clonic convulsions was reported at the three highest doses; other clinical signs included unsteady gait, excessive salivation and yellow staining on body surface area; necropsy did not indicate any abnormal findings; NOEL(M/F) = 5 mg/kg/day (based on excessive salivation and unsteady gait); **Supplemental;** (originally found acceptable by Berliner and McGee, 1/21/86; Leung, updated and revised to supplemental on 4/9/91; Leung, updated, 11/8/95).

#### REPRODUCTION, RAT

**\*\* 028, 035; 37546, 91522;** "Two Generation Reproduction Study in Rats" (International Research & Development Corp., Mattawan, MI, Study No. 406-024, 4/22/83); 834; RU 25474 (Batch 18, 98.5% purity); oral gavage; 0 (corn oil), 0.75, 3, or 12 mg/kg/day; 10-24 rats/sex/dose group/parental generation; decrease in mean body weight occurred in males at high dose in F-0 (82.1-90.5% of control,  $p < 0.05$ ) and F-1b (82.2-92.9% of control,  $p < 0.05$ ) generations; treatment-related reduction in pup weight occurred consistently in high dose group for F-1a, F-1b, and F-2 litters on days 4, 7, 14, and 21; **possible systemic adverse effect:** one F1 weanling from a litter in the mid dose group and 13 F1 weanlings from 3 litters in the high dose group exhibited convulsions prior to death; no test article related macroscopic or microscopic lesions and organ weight changes were reported; maternal NOEL  $\geq$  12 mg/kg/day (no effect at HDT), paternal NOEL = 0.75 mg/kg/day (decreased body weight gain), developmental NOEL = 3 mg/kg/day (decreased pup weight), systemic NOEL = 0.75 mg/kg/day (weanlings showing convulsions prior to death); study initially reviewed as unacceptable and not upgradeable; (Van Way and Aldous, 12/31/85); study was rereviewed with additional histopathology data on adult reproductive tissues and clinical observations; **acceptable;** (upgraded, Leung, 3/28/91).

028; 37547; "Perinatal and Postnatal Study in Rats" (International Research & Developmental Corp., Mattawan, MI, Study No. 406-038, 12/20/83); CD Rats; RU 25474 (Batch 18, 98.5% purity); oral gavage; 0 (corn oil), 0.5, 0.75, 3.0, or 12.0 mg/kg/day to 20 dams/dose on day 15 of gestation through day 20 of lactation; high dose dams exhibited reduced body weight gain (67% of control) during gestation days 15-20 but achieved parity during the lactation period; maternal clinical signs included excessive salivation seen in 3/20 dams treated at high dose; 100% mortality in 4 litters in the 12 mg/kg/day group; in one litter all pups were stillborn on day 0 and the remaining three litters all pups were dead prior to lactation day 4; significant decrease (86-90% of control,  $p < 0.05$ ) in pup body weight on lactation days 0 and 4; **no adverse effects indicated**; no treatment-related effects on the incidence of maternal necropsy findings, mean gestational length, parturition, uterine observations at weaning or pup appearance and behavior were reported in the treated groups; maternal NOEL = 3.0 mg/kg/day (body weight gain), developmental NOEL = 3.0 mg/kg/day (based on neonatal viability and growth); **Supplemental**; (Aldous, 1/13/86; updated, Leung, 4/10/91).

#### TERATOLOGY, RAT

\*\* 028, 038; 39; 37544, 91530; 93252; "Teratological Study in the Rat" (Centre de Recherches Roussel UCLAF, Romainville, FR, Study No. RU 4BE 80501-507/A, 6/25/80); 833; CD-1 rats; RU 25474 (Batch No. 29 3E-0281, 98.5% purity); oral gavage; 0 (corn oil), 2, 6, or 18 mg/kg/day to 21 - 22 females/dose on days 6 - 17 of gestation; **no adverse effects**; mortality: 4 deaths due to intubation error and 1 at high dose exhibited piloerection and sedation on gestation day 20 died the following day; no compound-related effects reported in appearance and body weight changes; slight increase in fetal loss as compared to control group but was not considered toxicologically significant because no dose relationship was evident and these values were within historical controls; no treatment-related changes in fetal body weights, sex distribution, and total number of litters with external or visceral abnormalities; maternal NOEL = 6 mg/kg/day (piloerection, sedation); developmental NOEL  $\geq$  18 mg/kg/day (no effect at HDT); initially reviewed as unacceptable but possibly upgradeable (Van Way and Aldous, 12/23/85; Leung, 3/26/91); study rereviewed with additional data indicating that the dosing solutions were prepared weekly; **acceptable**; (upgraded, Leung, 11/7/91).

#### TERATOLOGY, RABBIT

\*\* 038, 91529; "Developmental Toxicity Study in New Zealand White Rabbits", Project 603-002; International Research and Development Corp., 8/21/89; Tralomethrin technical grade product (RU 25474), 95.9% purity, lot# 7B0234B; Vehicle: corn oil; dose levels: 0, 6.25, 12.5 and 25 mg/kg/day; 16 females/dose; maternal effects included decreased body weight gain, decreased defecation and hair loss, no treatment-related fetal effects were observed; Maternal NOEL = 12.5 mg/kg/day (body weight gain, abortions), Fetal NOEL > 25 mg/kg/day; **No adverse effects, Acceptable**. (Morgan, 3/11/91).

028; 37545; "RU 25474 Teratological Study in the Rabbit" (Centre de Recherches Roussel UCLAF, Romainville, FR, Study No. RU 4BE 80506-508/A, 6/25/80); 833; New Zealand White rabbit; RU 25474 (Batch No. 12, Control No. 9E 0645); oral gavage; 0 (corn oil), 2, 8, or 32 mg/kg/day to 15 females/dose on days 6 - 18 of gestation; **no adverse effects indicated**; one litter in the control group showed 6 dead fetuses in utero; no treatment-related effects on litter parameters, fetal body weights, sex distribution, total number of litters with external or visceral abnormalities; maternal NOEL = developmental NOEL  $\geq$  32 mg/kg/day (no effect at HDT); incomplete fetal examination: half the fetuses were examined for visceral abnormalities and the remaining half were examined skeletally; inadequate justification in selecting dosage levels; study originally reviewed as **unacceptable** and **not upgradeable** (Van Way and Aldous, 12/23/85); **status unchanged**; (updated, Leung, 4/10/91).

#### GENE MUTATION

\*\* 029, 037; 37549, 91527; "Detection of a Mutagenic Potential - Bacterial Tests: Ames Test" (Roussel Uclaf, Seine, France, Study No. RU 4BE 80 28 07/A, 7/28/80); 842; RU 25474 (batch No. and purity not given); tested with Salmonella typhimurium strains TA 1535, TA 100, TA 1537, TA 1538, TA 98 with and without activation by aroclor 1254-induced rat liver S9 fraction; duplicate plates/dose; two trials; concentrations 0 (DMSO), 2, 10, 50, 200, 500, 1000, or 5000 ug/plate; precipitation occurred at concentrations > 100 ug/plate; 48 - 72 hr incubation at 37°C; positive controls functional; **no adverse effects**; no increase in frequency of revertants reported with or without metabolic activation; **acceptable**; (Shimer and Gee, 12/19/85; updated, Leung, 3/15/91).

**029; 37553;** "Mutagenicity Evaluation of RU 25474 in the Mouse Lymphoma Forward Mutation Assay" (Litton Bionetics, Inc., Kensington, MD, LBI Project No. 20999, 6/8/82); RU 25474 (Batch 18, 98.5% purity); tested with L5178Y TK +/- cells with and without activation by aroclor 1254-induced rat liver S9 fraction; triplicate plates/dose; 2 trials; 4 hr exposure followed by 2 or 3 days of expression time; concentrations of 0 (DMSO), 0.244, 0.488, 0.977, 1.95, or 3.91 ug/ml without S9 activation, concentrations of 0 (DMSO) and a dose range of 1.95 - 40.0 ug/ml with activation; **possible adverse effect indicated:** increase in mutation frequency reported in the 2nd trial with metabolic activation; 1st activation trial had many plates lost to contamination; mutagenic effect not confirmed; **unacceptable and not upgradeable;** (Shimer and Gee, 12/19/85; updated Leung, 4/15/91).

Summary: One acceptable gene mutation study employing the Ames test was submitted and no increase frequency of revertants was indicated. A second study using the Mouse Lymphoma Forward Mutation Assay reported an increase in mutation frequency in the presence of metabolic activation but this mutagenic effect was not confirmed by another trial.

#### CHROMOSOMAL EFFECTS

029, 037; 37550, 91527; "Detection of a Mutagenicity Potency: Micronucleus Test in Mouse" (Roussel Uclaf, Seine, France, Study No. RU 4BE 80 28 07/A, 7/28/80); 843; RU 25474 (batch no. 2, purity not given); oral dose given in two equal doses separated by an interval of 24 hours; 0 (sesame oil), 6, 12, or 24 mg/kg; 5 CD1 mice/sex/dose; bone marrow samples taken at 6 hours after second dose; 2000 polychromatic erythrocytes/mouse examined for micronuclei; **no adverse effects indicated;** no mortality; RU 25474 did not produce an increase in micronucleated polychromatic erythrocytes; no information on test article; no justification of dose levels selected; inadequate number of sampling times, inappropriate time of bone marrow sampling; **unacceptable and not upgradeable;** (Shimer and Gee, 12/19/85; updated, Leung, 3/15/91).

\*\* 029, 032, 037; 37552, 44437, 91528; "Analysis of Metaphase Chromosomes Obtained from Bone Marrow of Rats Treated with RU 25474" (Huntingdon Research Centre, Cambridgeshire, GB, Study No. RSL-4BE-571/821037/A, 12/2/82); RU 25474 (98.5% purity, Batch No 18, control number OE 0246); tested in Sprague Dawley CD rats; oral gavage; single dose: 0 (corn oil), 30, 60, or 120 mg/kg; 5 rats/sex/dose/ sacrifice time; 2 hrs prior to sacrificing at 6, 24, and 48 hrs, rats were treated with 4 mg/kg of colchicine (ip); 50 metaphase cells read per animal; mortality: 1 mid-dosed male and 2 high-dosed females died; clinical signs: hypopnea and lethargy observed one hr after dosing at mid and high dose; positive control functional; **no adverse effect indicated;** none of the treatment doses induced chromosomal aberrations that was significantly different from the control; **acceptable;** study originally reviewed and was found unacceptable but possibly upgradeable with submission of missing pages; (Shimer and Gee, 12/19/85; upgraded, Leung, 3/18/91).

029; 37551; "Mutagenicity Evaluation of RU 25474, Batch 18 in an In Vitro Cytogenetic Assay measuring Chromosome Aberration frequencies in Chinese Hamster Ovary (CHO) Cells" (Litton Bionetics, Inc., Kensington, MD, LBI Project No. 21000, 5/10/82); RU 25474 (Batch 18, 98.5% purity); tested in Chinese Hamster Ovary Cells with and without activation by aroclor 1254-induced rat liver S9 fraction; 100 cells/dose scored for chromosomal aberrations; single trial; no duplicates; concentrations 0 (DMSO) and a dose range of 0.1 - 333.3 ug/ml; 2 and 8 1/2 to 10 hr exposure with and without S9 activation, respectively; positive controls functional; **no adverse effects indicated;** no increase in aberrations reported; single harvest time, inadequate number of duplicates, no information on mitotic index, cell cycle delay, or cytotoxicity; **unacceptable and not upgradeable;** (Shimer and Gee, 12/19/85; updated, Leung, 4/12/91).

029; 37554; "Dominant Lethal Assay of RU 25474 in the Male Rat" (Reprotox, Huntingdon Research Centre, Munster, Germany, Study No. 940/6/81, 1/21/82); RU 25474 (Batch 18, 98.5% purity); 22 Sprague Dawley males rats/group given 0 (corn oil), 1, 4, or 12 mg/kg/day by intragastric intubation for 10 weeks and then mated 1:1 per week for four weeks; mortality: 3 in the control group and 1 in the low dose group; Clinical signs including unsteady gait, impaired use of hindlimbs, body tremors (1 male), hunched posture and piloerection observed during first nine days of dosing in males receiving 12

mg/kg/day; no treatment-related macroscopic changes at terminal necropsy; mating performance of males not affected at any of the 4 pairings; no significant differences ( $p > 0.05$ ) in mean values for number of implantations, viable embryos, early and late embryonic deaths, pre- and post-implantation losses; no positive concurrent controls; no analyses of dosing solutions; **unacceptable and not upgradeable**; (Shimer and Gee, 12/19/85; updated Leung, 4/16/91).

\*\* 037; 91525; "Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells" (Microbiological Associates, Inc., Rockville, MD, Lab. Study No. T8225.337003, 10/24/88); 843; Tralomethrin Technical (batch 54, 96.6% a.i.); tested in Chinese Hamster Ovary Cells with and without activation by aroclor 1254-induced rat liver S9 fraction; 100 cells from each duplicate/dose scored for chromosomal aberrations; single trial; concentrations 0 (acetone) and a dose range of 0.7 - 50 ug/ml; 2 and 18 hours exposure with and without S9 activation, respectively; positive control functional; **no adverse effects**; Tralomethrin Tech did not induce any significant increases in the frequencies of cells with structural aberrations in the absence or presence of metabolic activation ; **acceptable**; (Leung, 3/7/91).

#### DNA DAMAGE

029, 037; 37548, 91527; "Detection of a Mutagenic Potential - Bacterial Tests: Growth Inhibition Test" (Roussel Uclaf, Seine, France, Study No. RU 4BE 80 28 07/A, 7/28/80); RU 25474 (batch 10); tested with E. Coli strains W 3110 (thy<sup>-</sup> pol A<sup>+</sup>), p 3478 (thy<sup>-</sup> pol A<sup>-</sup>), WP 2 (trp<sup>-</sup> uvrA<sup>+</sup> exrA<sup>+</sup>), and CM 611 (trp<sup>-</sup> uvrA<sup>-</sup> exrA<sup>-</sup>) without activation; concentrations 0 (DMSO) and a dose range of 500 - 10000 ug/ml, 0.1 ml, into each of 9 wells in agar plate with 81 holes, 10 mm in diameter; comparison of growth inhibition by tralomethrin between wild type E. Coli strains and their mutants; 18 hr exposure at 37<sup>0</sup> C; positive control functional; **no adverse effects indicated**; RU 25474 had the same effect on E. Coli parent strains and their mutants; RU 25474 did not exhibit any mutagenic activity; purity of RU 25474, stability of RU 25474 in DMSO, actual dose levels, and individual data not reported, metabolic activation not included in trial, poor description of protocol, and no justification of dose level; **unacceptable and not upgradeable**; (Shimer and Gee, 12/18/85; updated, Leung, 3/8/91).

\*\* 037; 91526; "Unscheduled DNA Synthesis in Rat Primary Hepatocytes" (Microbiological Associates, Inc., Rockville, MD, Lab. Study No. T8225.380, 9/29/88); 844; Tralomethrin Technical (batch 54, 96.6% a.i.); tested with primary Fischer 344 rat hepatocytes without activating system; concentrations 0 (acetone) and a dose range of 50 - 5000 ug/ml; precipitation occurred at  $\geq 150$  ug/ml; 50 nuclei scored from each of three coverslip cultures/dose; single trial; 18 - 20 hour exposure in the presence of <sup>3</sup>H-thymidine (10 uCi/ml); positive controls functional; **no adverse effects**; test article did not cause a significant increase in unscheduled DNA synthesis; **acceptable**; (Leung, 3/8/91).

#### NEUROTOXICITY

002, -032, -033; 37514, 44435, 91518; "The Acute Delayed Neurotoxicity of RU 25474 to the Domestic Hen" (Huntingdon Research center, Cambridgeshire, GB, Reference No. RSL 422 NT/80632, 9/4/80); hens; 817; RU 25474 (Lot 18, 98.5% purity); oral gavage; O (corn oil), TOCP (500 mg/kg, positive control), 1500, 3000, or 6000 (2 groups) mg/kg to 10 hens/dose group for 21 days; LD<sub>50</sub> > 6000 mg/kg; mortality : 1/10 and 4/20 in hens treated with 0 and 6000 mg/kg, respectively; positive control functional with all hens showing signs of ataxia and 3 hens were sacrificed prior to termination due to severity of ataxia; **no adverse effects indicated**; no signs of neurotoxicity were reported in any of negative control or other test groups; no repeat dosing after 21 days was conducted as required since no signs of neurotoxicity were observed during the first period of 21 days; study originally reviewed and was found incomplete and unacceptable (Gee, 12/20/85); study rereviewed with submission of missing tables; status unchanged; **unacceptable and not upgradeable**; (Leung, 3/4/91).